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EXAMINER
SHAHNAN SHAH, KHATOL S

ART UNIT	PAPER NUMBER
1645	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/646,043	Applicant(s) HAKALEHTO, EINO ELIAS	
	Examiner Khatol S Shahnan-Shah	Art Unit 1645	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2002 and 02 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-17 and 19 -26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-17 and 19-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/02/2002 has been entered.

2. Amendment D received 9/30/2002, paper 20 is acknowledged. Claim 18 was canceled. Claims 14, 19 and 20 were amended.

3. Currently claims 14-17 and 19-26 are pending and under consideration.

Prior Citations of Title 35 Sections

4. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior office action.

Objections Withdrawn

5. Objection made in paragraph 4 of the office action mailed 7/05/2001, paper # 15 is withdrawn. The office has received an Abstract of Disclosure located on a separate sheet attached to this response.

6. Objection to claim 20 for not reciting sequence identification number made in paragraph 12 of the office action mailed 3/29/2002, paper # 18 is withdrawn.

Rejections Moot

7. Rejection of claim 18 made under 35 USC 112-first paragraph in paragraph 13 of the office action mailed 3/29/2002, paper # 18 moot in view of applicant's cancellation of the claim.

8. Rejections of claim 18 made under 35 USC 102(b) in paragraphs 15 of the office action mailed 3/29/2002, paper # 18 is moot in view of applicant's cancellation of the claim.

9. Rejections of claim 18 made under 35 USC 103(a) in paragraphs 16 of the office action mailed 3/29/2002, paper # 18 is moot in view of applicant's cancellation of the claim.

Rejections Withdrawn

10. Rejection of claims 14-17 and 19- 26 under 35 U.S.C. 112, first paragraph made in paragraph 13 of the office action mailed 3/29/2002, paper # 18 is withdrawn in view of applicant's amendments.

11. Rejections of claims 14-17 and 19- 26 made under 35 USC 102(b) in paragraphs 15 of the office action mailed 3/29/2002, paper # 18 is withdrawn in view of applicant's amendments.

12. Rejections of claims 14-17 and 19- 26 made under 35 USC 103(a) in paragraphs 16 of the office action mailed 3/29/2002, paper # 18 is withdrawn in view of applicant's amendments.

Rejections Maintained

13. Rejection of claims 14-17 and 19-26 under 35 U.S.C. 112, second paragraph made in paragraph 14 of the office action mailed 3/29/2002, paper # 18 is maintained.

The rejection was as stated below:

Claims 14-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 recites the limitation "detecting antigens which are expressed soon after inoculation". It is not clear what time period between 3 to 10 hours constitutes this phase.

Claim 14 recites the limitation "before actual growth phase". It is not clear what time period between 3 to 10 hours constitutes this phase.

Claim 14 recites the limitation "in the beginning of the growth phase". It is not clear what time period between 3 to 10 hours constitutes this phase.

Applicant's arguments of 09/30/ 2002 have been carefully considered but they are not deemed persuasive.

Applicant argues that one of ordinary skill in the art would know without undue experimentation when each of the time period begins. It is not necessary to define the time periods in numerical real time.

It is the examiner's position the growth phase differs among different organisms and highly dependent on culture conditions, i.e., temperature, type of medium, size of inoculum, etc. It also is not clear if one assays at constant intervals, then correlates with growth. What is the definition of "actual growth phase" and what is meant by recitation of "actual growth phase"? Thus one of ordinary skill in the art would not know without undue experimentation when each of the time periods begins. The above terms are not defined by the claims or in the specification and the phrases are not descriptive.

New Grounds for rejections

Claim Rejections - 35 USC § 112- first paragraph

14. Claims 14-17 and 19-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting *Salmonella* species from a cultivation medium, does not reasonably provide enablement for all bacteria having fimbriae. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Amended claim 14 recites a method for detecting bacteria having fimbriae, comprising detecting bacteria having fimbriae from a cultivation medium within the time period of 3 to 10 hours from the onset of cultivation, by detecting fimbrial antigens, which are, expressed soon after inoculation into the medium. The claim language encompasses any bacteria having fimbriae and any fimbrial antigen. However, the specification is directed towards detecting *Salmonella* in foodstuff. (see page 3) The specification mainly mentions two strains *Salmonella typhimurium* and *Salmonella enteriditis* that are the cause of food-borne disease (page 6). In example 4 specification recites the use of RVS broth as growth medium (page 4, line 9). In the same line it is mentioned that the plate cultures were started simultaneously with ELISA measurements, it's not clear which medium was used to plate the organism and how bacterial densities were measured. The specification fails to provide essential information and steps. There is not enough guidance in regard to the production of antibodies against different fimbrial antigens of other bacteria or other enteric bacteria and their similarity or differences with the *Salmonella.*

It is well known in the art that fimbriae are thin, proteinaceous, polymeric surface organelles expressed by the members of Enterobacteriaceae including most *Salmonellas*. The adhesive function of Particular fimbriae of *E.coli* has been well studied. However the role of *Salmonella* fimbriae is not well understood (Dibb-Fuller, Letters in Applied Microbiology 1997. Prior art already made of record). There are many different fimbriae known to be expressed by *Salmonella*, (i.e. SEF 14, 17, 21 etc) (Dibb-Fuller page 451). Also, little information is available on the *invitro* conditions of expression of these fimbriae (Dibb-Fuller page 447).

Factors to be considered in determining whether a disclosure would require undue experimentation have been reiterated by the court of appeals in In re Wands, 8 USPQ 2d 1400 at 1404 (CAFC 1988).

These factors include 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, and 8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other bacteria and their antigens having the claimed functional feature of *Salmonella* fimbrial antigens, 3) there are no working examples which suggest the desired results can be obtained in other bacteria, 4) the nature of the invention involves the complex and incompletely understood area of rapid detection methods, 5) the state of the prior art shows the lack of correlates to bacterial fimbrial antigens, 6) the relative skill of those in the art is commonly recognized as quite high (post – doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

Amended claim 20 of the instant application is not only drawn to a synthetic polypeptide but is also drawn to a derivative thereof. The specification discloses an 18 amino acids sequence (SEQ ID #1 (see amendment A). The amended specification recites that this sequence was traced from the *Salmonella typhimurium* type 1 fimbriae and in order to select a specific

sequence differing from the corresponding *E. coli* type 1 fimbriae, the two sequences were compared with each other. There is no guidance provided as to how different these sequences were from each other.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of peptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein or a peptide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of prediction protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is **not** routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure.

One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. Multiple substitutions.

The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins.

The specification does not support the broad scope of the claim 20, which encompass all modifications and fragments because the specification does **not** disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;
- what derivatives or fragments, if any, can be made which retain the biological activity if the intact protein; and
- the specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicant have **not** provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of derivatives of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the proteins structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen Inc v. Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed.Cir.1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S.P.Q. 546(Bd. Pat. App. & Int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the invention commensurate in

scope with the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

15. Claims 15-16, 19-20 and 24-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and16 recite the phrase "wherein bacterial antigens are detected". This broadens the scope of amended claim 14, which is directed to only " fimbrial antigens".

Claim 20 recites the phrase "wherein microbial antigens are detected". This broadens the scope of amended claim 14, which is directed to only " fimbrial antigens".

Claim 19 recites the limitation "fimbrial proteins". There is insufficient antecedent basis for this limitation in the claim. Claim 19 depends from claim 14, which recites "fimbrial antigens". It is not clear from the language of the claims if the antigen is only made of protein?

It is not clear what applicant intends in recitation of the term "comparable" in claim 19.

Claim 24 recites the phrase "wherein the bacteria incubated prior to detection at their optimal growth temperature". This is unclear because if one does not know what bacteria he/she has in the sample, how does one know what is the "optimal growth temperature" for the unknown bacteria?

It is not clear what constitutes the metes and bound of "about" 37 °C in claim 25.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 14-17 and 19-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thorns, C. J. et al. (US Patent Number 5,510,241) prior art already made of record, in view of Blakburn, C. de W. (Journal of Applied Bacteriology, Vol. 75, pp. 199-214, 1993).

Claims as amended now recite a method for detecting bacteria having fimbriae, comprising detecting bacteria having fimbriae from a cultivation medium within the time period of 3 to 10 hours from the onset of cultivation, by detecting fimbrial antigens, which are, expressed soon after inoculation into the medium.

Thorn et al. teach a method for detecting for the presence of *Salmonella* species expressing fimbrial antigens, which have been grown on a selected medium. (see title and abstract and claims). Thorn et al. used a variety of liquid and solid media (see column 2, lines 25-65) and various temperature ranges from 22°C to 60° C (see columns 5 and 6). Thorn et al. teach detecting bacteria having fimbriae from a cultivation medium within the time period of 18 hours from the onset of cultivation (see column 7, example I). Thorn et al. also used direct binding and indirect ELISA methods. Thorn et al. further teach a method wherein the microbial antigens are detected with antibodies, which have been produced against synthetic peptides or a derivative thereof (see column 11 and claims). Thorn et al. also teach

derivatives of the claimed synthetic peptide (see SEQ ID # 1, (i.e. amino acid 165-167) columns 26-28). Thorn et al. fails to teach time period of 3 to 10 hours from the onset of cultivation

However, attempts to reduce the incubation periods of either pre-enrichment of selective enrichment to 6- 8 hours for rapid methods of detection is routine in the art of microbiology (see Blakburn, page 199, Rapid Cultural Techniques).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the rapid method of screening taught by and the method taught by Thorn et al. to obtain the instant disclosure. Given the fact that rapid screening methods for bacteria such as *Salmonella* are needed. One having ordinary skill in the art would have been motivated by expectation of success and the attainment of a better method to obtain a method which shortens the cultivation period for detecting bacteria such as *Salmonella* which are a major cause of food poisoning. New approaches should be rapid, so that results can be obtained and appropriate action can be taken within a shorter period.

Conclusion

17. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is (703) 308-8896. The examiner can normally be reached on 7:30 AM - 4 PM from Monday through Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned to is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Khatol Shahnan-Shah, BS, Pharm, MS

Biotechnology Patent Examiner

Art Unit 1645

March 27, 2003

RODNEY P SWARTZ, PH.D
PRIMARY EXAMINER